IJNRD.ORG ISSN : 2456-4184
INTERNATIONAL JOURNAL OF NOVEL RESEARCH AND DEVELOPMENT (IJNRD) | IJNRD.ORG
An International Open Access, Peer-reviewed, Refereed Journal

PREDNISOLONE INDUCED IATROGENIC CUSHING'S SYNDROME

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Abstract: Cushing's syndrome is a rare disorder which occurs due to excessive levels of cortisol in the blood. The following case study depicts a female patient who was suffering from a dermatologic allergy for which she has been consuming prednisolone orally for long time, which resulted in serious adverse event which is iatrogenic Cushing's syndrome induced by prednisolone. This contributes to provide an insight in prescribing pattern of steroids as they are associated with severe adverse drug reactions upon chronic usage. The symptoms exhibited include moon facies, hump over the neck, purple striae on the abdomen, central obesity, tiredness, giddiness. The treatment usually includes stopping the medication consumption to aid in faster recovery and alleviate the symptoms by providing relief.

Introduction: This case report presents a rare occurrence of Iatrogenic Cushing syndrome due to administration of prednisolone. One of the main causes of Cushing's syndrome is extended periods of exposure to elevated levels of cortisol in the bloodstream. Endogenous Cushing's syndrome occurs when the adrenal glands produce an excessive amount of cortisol. It is classified as ACTH-dependent and ACTH-independent [1]. The development of Iatrogenic Cushing's syndrome (ICS) is often associated with the prolonged use of oral or parenteral steroids at high doses [2]. The traditional view of the disease, which involves a noticeable combination of trunk obesity and limb wasting, rounded face and reddish complexion, excessive body hair growth with balding at the forehead, muscle weakness, easy bruising, fractures in the vertebrae, high blood pressure, and diabetes, is not as frequently observed in modern times. The pattern of fat distribution can provide helpful clues, as Cushing's syndrome often presents with an excess of visceral fat leading to central or truncal obesity, accumulation of fat in the cheeks and temporal areas of the face (referred to as "moon face"), dorsocervical area (known as "buffalo hump"), and fat pads above the collarbones (supraclavicular fat pads). Additional signs that may be more indicative of Cushing's syndrome include weakness in the muscles close to the body (proximal myopathy), wide and purplish stretch marks (striae), weakened bones (osteoporosis), thinning of the skin, and increased susceptibility to bruising [3]. Cushing's syndrome is a rare condition that arises from an extended period of being exposed to an excessive amount of glucocorticoids [4]. The primary cause of Cushing's syndrome, known as exogenous or iatrogenic Cushing's syndrome, is the administration of glucocorticoids in doses that surpass normal physiological levels. Since glucocorticoids are employed in the treatment of inflammatory, autoimmune, and neoplastic conditions, it is crucial to obtain a comprehensive record of medication usage [4]. The key to diagnosing Cushing's syndrome is to first confirm the presence of hypercortisolism through laboratory tests, before proceeding with tests to determine the underlying cause. Cushing's syndrome is characterized by elevated levels of cortisol in the blood, as well as disruption of the body's normal daily rhythm of cortisol secretion and feedback in the hypothalamic-pituitary-adrenal (HPA) axis. These are the primary biochemical indicators of the disorder. Under normal circumstances, cortisol is released in a predictable, 24-hour cycle, with peak levels occurring in the early morning and reaching their lowest point around midnight (at less than 50 nmol/L or 1.8 µg/dL). In individuals with Cushing's syndrome,

this natural rhythm is disrupted, with most patients still exhibiting normal cortisol levels in the morning, but elevated levels at night. As a result, measuring cortisol levels at midnight is typically the most useful diagnostic approach. Although measuring free serum cortisol can be challenging, levels of salivary cortisol or total serum cortisol are commonly used instead [3]. This method is considered the definitive test for differentiating between Cushing's disease and non-pituitary sources of ACTH secretion. It involves the insertion of catheters into the inferior petrosal sinuses, which drain blood from the pituitary gland. A pre-CRH or post-CRH gradient of 2:1 or higher from the central (inferior petrosal) to peripheral plasma ACTH is indicative of Cushing's disease [3]. Gradually tapering exogenous steroids is the most effective treatment for iatrogenic Cushing's syndrome. The long-term use of steroids can suppress the function of the adrenal glands, and it may take several months for adrenal function to return to normal. Thus, a slow tapering of steroids is recommended to allow the adrenal function to recover [1].

This case report provides valuable insights into the significant adverse events that can arise from long-term use of prednisolone, a corticosteroid medication. It serves as a reminder to physicians to exercise caution when prescribing prednisolone for extended periods, as it has been linked to the development of Cushing's syndrome. This report aims to increase awareness among healthcare professionals regarding the potential risks associated with prolonged administration of prednisolone.

Case presentation: A 23-year-old female patient who sought medical attention due to a range of distressing symptoms. The patient's chief complaints included burning micturition lasting for the past 10 days, reddish discoloration of urine, and persistent vomiting episodes multiple times a day for the past 15 days, with the vomitus appearing white in color. The patient also reported experiencing pain in the left hypochondrium of the abdomen along with fever for the past 15 days. The fever was characterized as high grade and accompanied by chills and rigors. Furthermore, the patient exhibited a decrease in appetite, weakness, giddiness, and reduced food intake over the same 15-day period. Notably, the patient had a history of facial puffiness, which had been present for the past 3 months.The patient had a past medical history of a dermatologic condition, for which she had been prescribed clobazam 0.03% ointment and prednisolone tablets. Additionally, she had a history of urinary tract infection (UTI), accompanied by symptoms of fever and a dry cough.

On examination, the patient was found to be conscious and coherent. She was afebrile with a PR: 100 beats per minute, BP: 110/80 mmHg, Cardiovascular examination revealed audible S1 and S2 sounds, Respiratory system examination indicated bilateral air entry, abdomen appeared soft upon palpation, CNS examination did not reveal any focal neurological deficits. Additionally, the patient presented with moon facies and a hump over the neck. Purple striae were observed on the abdomen, accompanied by Central obesity, thin skin, and hyperpigmented patches. Dermatitis was also present.

Laboratory data: Laboratory investigations indicated her sodium levels as 149 mmol/L, potassium levels as 2.8 mmol/L, and chloride levels as 117 mmol/L. The glucose levels- 316mg/dL, calcium lactate- 7.5 mg/dL, blood urea- 11.6 mg/dL, serum creatinine- 1.0 mg/dL, SGPT- 40.8, SGOT- 36.9, ALP- 135, and total serum proteins- 4.9 g/dL. Additionally, her albumin level was 1.7 g/dL, direct bilirubin was 1.1 mg/dL, and total serum bilirubin was 2.2 mg/dL. Her arterial blood gas (ABG) analysis revealed a pH of 7.464, a PCO2 level of 23.9 mmHg, and a PO2 level of 88.3 mmHg.

Based on chief complaints, thorough physical examination, laboratory findings and studying previous medical history and medication history it was confirmed that the patient was suffering with ‘Prednisolone Induced Iatrogenic Cushing Syndrome’.

Treatment:

The patient was prescribed with a treatment regimen that includes injection Ciprofloxacin 100ml IV BD, along with injection Pantoprazole 40mg IV OD, injection Ceftriaxone 1g IV BD. Additionally, she was prescribed with Syrup Citralka 10ml mixed with half a glass of water BD, and if necessary, she could take tablet Paracetamol 500mg, as needed for pain relief, to address nausea/ vomiting, she received injection Ondansetron 4mg IV BD. In terms of IVF, she received 1 unit each of normal saline, Ringer lactate, and dextrose normal saline at a rate of 75cc/hr. As nutritional supplementation, she was informed to take Tablet MVT orally OD. She was advised to take tablet Calcium& Vitamin D3 orally OD. The administration of prednisolone was ceased by gradually reducing the dosage and subsequently discontinuing its consumption to prevent further damage and aid in quick recovery.

Discussion: Cushing's disease, which affects approximately 40 out of every 1,000,000 people, is more commonly observed in women, with a sex ratio of 9:1 [5]. The adrenal cortex's zona fasciculata synthesizes cortisol, which is a steroid hormone. Once synthesized, cortisol is transported to various areas of the body by a protein called cortisol

binding protein to which about 90% of cortisol binds. As a result, cortisol has a bioavailability range of 60% to 100%. Excessive level of cortisol in the body leads to a rise in gluconeogenesis, glycogenolysis, and insulin resistance. As a steroid hormone, cortisol influences the transcription and translation of enzymes responsible for the metabolism of fats, glycogen, protein synthesis, and Kreb's cycle. It stimulates the generation of free glucose in the body, causing a rise in blood sugar levels, and at the same time, increases insulin resistance. Extended protein catabolism is responsible for various symptoms, such as osteoporosis, purplish striae of the torso, and slow wound healing. These conditions involve the degradation of collagen, a protein composed of three amino acids. Furthermore, elevated levels of cortisol can lead to immune disturbances, resulting in a reduction in lymphocyte levels and an increase in neutrophils. The downregulation of NF-kappaB, AMP kinase, glycogen phosphorylase, superoxide dismutase, and various other enzymes are regulated by corticosteroids. IL-2, TNF alpha, IFN alpha, and gamma production are inhibited by cortisol. Consequently, low IL-2 levels can impede the multiplication of T-lymphocytes [1]. Elevated levels of cortisol have been linked to a higher risk of death caused by metabolic, cardiovascular, psychiatric issues, or infections [5]. Regardless of age, individuals with Cushing's disease often experience osteoporosis (40%) and fractures, particularly vertebral compression and spinal injuries. Consequently, it is crucial to include a comprehensive and extended treatment strategy for osteoporosis in patients diagnosed with Cushing's disease [5].

In this case the patient was suffering from dermatologic condition for which she consumed tablet prednisolone. Longterm administration of corticosteroids is associated with development of cushingoid symptoms and she developed moon facies, purple striae over her abdomen, hump over the neck, central obesity, with symptoms of tiredness, facial puffiness, giddiness and vomiting's. The main objective of presenting this case is to increase awareness among medical professionals regarding the significant adverse effects that can arise upon long-term steroid consumption. We aim to encourage medical professionals to exercise caution when prescribing steroids and to thoroughly assess the risk-to-benefit ratio before making a decision.

Conclusion: Although considered safe existing studies reveal that prednisolone has the potential to cause serious adverse drug reactions like Cushing’s syndrome on chronic use. The prescribers should consider risk to benefit ratio before prescribing prednisolone for long term usage. The only effective treatment strategy in treating Iatrogenic Cushing’s syndrome is to stop the administration of the causative drug, as prednisolone is a steroidal medication stopping it abruptly may lead to unwanted effects and to avoid such effects the dose of prednisolone is tapered and then stopped.

Abbreviations:

1. ACTH- Adrenocorticotropic hormone
2. CRH- Corticotropin releasing hormone
3. HPA- Hypothalamic pituitary adrenal axis
4. SGOT- Serum glutamic oxaloacetic transaminase
5. SGPT- Serum glutamic pyruvic transaminase
6. ALP- Alkaline phosphatase
7. PCO2- Partial pressure of carbon dioxide
8. PO2- Partial pressure of oxygen

Acknowledgement: The authors sincerely convey their gratitude towards the faculty members for their valuable support in presenting this case report.

Conflict of interest: The authors declare no conflict of interest.

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